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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4-32583A/USN		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/07739	16.07.2003	17.07.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K31/166		
Applicant		
NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.12.2003	02.09.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07739

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-15 as originally filed

Claims, Numbers

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1,2,4-8,10-13 (all in parts)

   because:

   ☒ the said international application, or the said claims Nos. 12, 13 (with respect to IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1,2,4-8,10-13 (all in parts)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	10,11 (1-9,12-13 no opinion)
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 12 and 13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Claims 1,2,4-8 and 10-13 all relate to a large number of compounds, defined by the term "modified amino acid". Although said claims involve any compound falling under said definition, it is recognized that only a small part of the claimed compounds are supported by the description under the provision of Art. 6 PCT and disclosed therein ounder the provision of Art. 5 PCT.
Under Rule 66.1(e) PCT, a preliminary examination is not carried out on matter which has not been searched. Therefore, the preliminary examination has been carried out on the whole subject-matter of claims 3 and 9, and on the parts of claims 1, 2, 4-8 and 10-13 that have been searched.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: US 5,563,158
   D2: US 5,866,536 (cited in the application)
   D3: WO 00/59863 (cited in the application)
   D4: WO 02/45754
   D5: LEONE-BAY A ET AL: 'ORAL DELIVERY OF BIOLOGICALLY ACTIVE PARATHYROID HORMONE' PHARMACEUTICAL RESEARCH, NEW YORK, NY, US, vol. 18, no. 7, July 2001 (2001-07), pages 964-970,

2. Novelty
   D1 discloses the use of modified amino acids for the inhibition of platelet aggregation. The compounds of formula I include compounds having a carbon

atom where a carboxyl and an amine function are attached (see end products of reaction schemes I, IV, VII, IX, X, XI, XII, where the definition of R includes H, therefore representing a carboxyl group, and where the definition of E includes an amine according to the specifications of R^9. See also compounds of Tables 3, 4), also in combination with other therapeutic agents such as heparin (column 3, line 16 - column 20, line 20; column 80, line 60 - column 85, line 43). **D1** anticipates therefore the subject-matter of claims 1, 2, 4, 6-8,and 10-13 of the present application.

D2 discloses compositions comprising modified amino acids, in combination with active agents such as heparinoids, calcitonin etc.(abstract; column 1, line 43 - column 2, line 5; column 2, line 49 - column 18, line 46; Examples 34-37 and 44-58; claims 1-22).

In interpreting claims for determining novelty, non-distinctive characteristics of a particular *intended use* (see claim 10: for the inhibition of platelet aggregation) should be disregarded (Guidelines IV.-7.6). Hence, the subject matter of claims 10 and 11 discloses nothing more than the composition per se. Claims 10 and 11 are therefore anticipated by D2. Furthermore, since D2 discloses pharmaceutical compositions comprising said modified amino acids AND heparin (see example 44), said composition was clearly applied for the inhibition of platelet aggregation. Since the present wording of claim 1 does not exclude the presence of an additional active ingredient, the subject-matter of claims 1-5, 9 and 12-13 are implicitly disclosed by D2.

D3 discloses pharmaceutical compositions comprising modified amino acids such as 5-CNAC, SNAD or SNAC, for the delivery of active agents such as heparin. For the same reasons as listed for D2, D3 anticipates the subject-matter of claims 1-4 and 10-13 of the present application.

D4 discloses pharmaceutical compositons in the form of tablets comprising salmon-calcitonin in combination with 5-CNAC (Example 4), and is therefore novelty-destroying for claims 10-11.

D5 discloses compositions comprising parathyroid hormone and 4-MOAC (abstract), and is thus novelty-destroying for claims 10 and 11.

3. **Industrial Applicability**

For the assessment of the present claims 1-9 and 12-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may

allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Further Objections

Claim 4 and all claims referring to claim 4 are not clear, since the pharmaceutical compositions that the use refers to comprise heparin, insulin, calcitonin or PHT (with reference to claim 2), however, the use refers to administration to a mammal receiving heparin, insulin, PTH or calcitonin treatment (in addition to the claimed use, where the same medicament is administered again).